Regulating Treg Cells at Sites of Inflammation

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Regulatory T (Treg) cells are emerging as common components in the development of immunity to both self and foreign antigen. With their ubiquitous participation comes the need to regulate the regulators to ensure protective immunity proceeds. Previous studies suggest that the very cofactors that boost an immune response to infection, such as Toll-like receptor (TLR) ligands and inflammatory cytokines (Pasare and Medzhitov, 2003), also downmodulate Treg cell function. Therefore, defining the key molecular players in the reciprocal regulation of effector and Treg cell function at sites of inflammation becomes critical to understanding autoimmune and infectious pathologies.

In the May 2008 issue of *Immunity*, Tang et al. (2008) proposed a model for the local loss of immune regulation in the diabetic pancreas of the nonobese diabetic (NOD) mouse (Tang et al., 2008). Treg cells can be demonstrated to have protective effects on the development of diabetes in the NOD mouse, but it remains unclear whether a loss in Treg cell function is causative in disease progression. The study revealed a striking difference in expression of CD25 by Foxp3$^+$ Treg cells in the draining lymph node versus that by the cells in the pancreas of diabetic mice. Foxp3$^+$ Treg cells in the inflamed pancreas expressed markedly less CD25 than their lymph node counterparts. The authors proposed that the genetic defects in IL-2 production in the NOD (Yamanouchi et al., 2007) led to the loss of CD25 expression and thereby compromised Treg cell survival. In support of this notion, boosting Treg cell numbers and their expression of CD25 with low-dose IL-2 treatment prevented diabetes progression.

The reduction in CD25 expression by Treg cells in the diabetic pancreas was an important observation but prompted questions as to whether this potential control mechanism for Treg cells was a more general consequence of the inflammatory milieu. With a keen interest in the regulation of CD4 effector function at tissue sites of inflammation (Katzman and Fowell, 2008), we have analyzed the expression of CD25 by Foxp3$^+$ Treg cells in the dermis of non-NOD mouse strains after a number of immune challenges including *Leishmania major* and OVA-CFA (ovalbumin-complete Freund's adjuvant) in the dermis and influenza in the lung. With notable similarity to the NOD pancreas, we found that reduced expression of CD25 by Foxp3$^+$ Treg cells was a general phenomenon in inflamed tissues of BALB/c (Figure S1 available online) and C57BL/6 mice. We conclude that the reduced CD25 expression by Foxp3$^+$ T cells in the diabetic pancreas is neither autoimmune nor NOD specific. Nonetheless, it will be important to determine whether reduced IL-2 production, the mechanism proposed for the CD25 modulation by the authors, is common to these other inflammatory sites.

Our results extend the observations made by Tang et al. (2008) to highlight a common Treg cell phenotype at sites of inflammation. Further dissection of the components that are within the inflammatory milieu and that regulate CD25 expression is required, and confirmation that the loss of CD25 compromises Treg cell function is necessary. On a cautionary note, the ability of human CD4$^+$ T cells to transiently upregulate Foxp3 without the acquisition of regulatory function raises the possibility that the CD25^{lo} Foxp3$^+$ cells we find accumulating at sites of inflammation may not derive from CD25^{hi} Foxp3$^+$ Treg cells. Establishing the lineage relationship of the CD25^{lo} cells to the CD25^{hi} cells will be critical. Thus, the fate of Foxp3$^+$ Treg cells on entry into inflamed sites remains unclear but well worth pursuing.

SUPPLEMENTAL DATA

Supplemental Data include one figure and can be found with this article online at http://www.immunity.com/supplemental/S1074-7613(08)00428-7.

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